

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 December 2003 (18.12.2003)

PCT

(10) International Publication Number
WO 03/103649 A1

(51) International Patent Classification⁷: A61K 31/085 (74) Agent: ÖHMAN, Ann-Marie; Hormos Medical Corporation, Itäinen Pitkäkatu 4 B, FIN-20520 Turku (FI).

(21) International Application Number: PCT/FI03/00369 (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date: 14 May 2003 (14.05.2003) (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(25) Filing Language: English (30) Priority Data: 60/385,904 6 June 2002 (06.06.2002) US

(26) Publication Language: English

(71) Applicant (for all designated States except US): HORMOS MEDICAL CORPORATION [FI/FI]; Itäinen Pitkäkatu 4 B, FIN-20520 Turku (FI).

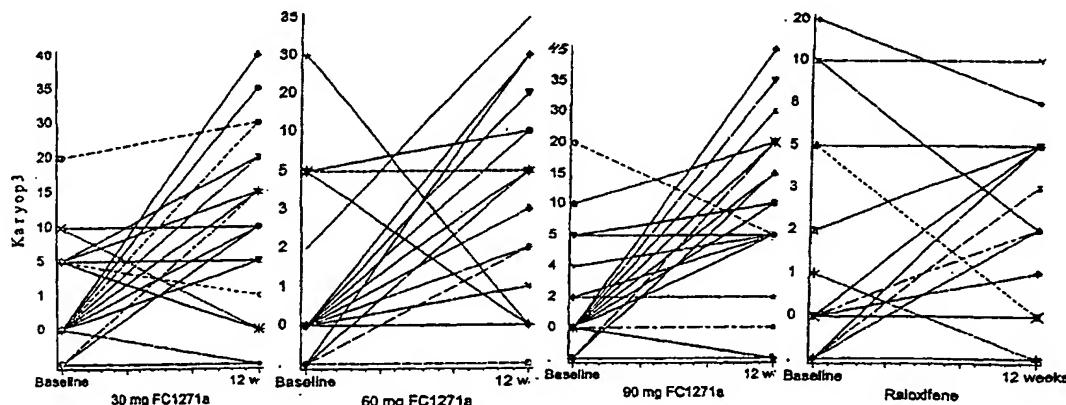
(72) Inventors; and (75) Inventors/Applicants (for US only): BLOM, Taru [FI/FI]; Perkontie 16, FIN-21270 Nousiainen (FI). GRÖNROOS, Paula [FI/FI]; Nyrykinkatu 1, FIN-20540 Turku (FI). HALONEN, Kaija [FI/FI]; Niittytie 10, FIN-21290 Rusko (FI). HÄRKÖNEN, Pirkko [FI/FI]; Vuorelantie 3 B 43, FIN-20720 Turku (FI).

Published:

— with international search report

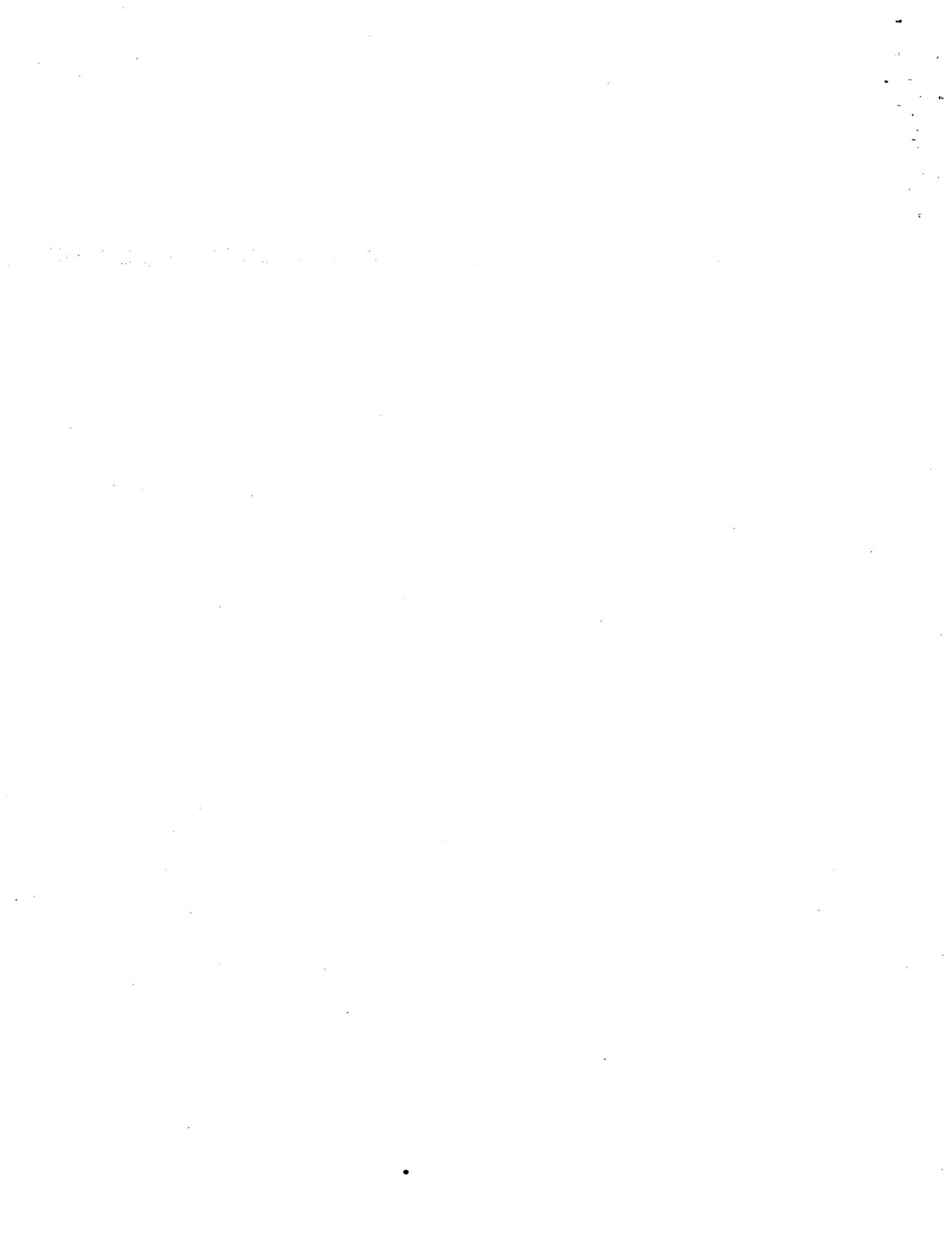
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD FOR THE INHIBITION OF ATROPHY OR FOR TREATMENT OR PREVENTION OF ATROPHY-RELATED SYMPTOMS IN WOMEN



WO 03/103649 A1

(57) Abstract: This invention relates to a method for inhibition of skin atrophy, or epithelial or mucosal atrophy in women, or to a method for treatment or prevention of symptoms related to atrophy, said method comprising administering to the woman an effective amount of the compound of formula (I) or a geometric isomer, a stereoisomer, a pharmaceutically acceptable salt, an ester thereof or a metabolite thereof.



METHOD FOR THE INHIBITION OF ATROPHY OR FOR TREATMENT
OR PREVENTION OF ATROPHY-RELATED SYMPTOMS IN WOMEN

FIELD OF THE INVENTION

5

This invention relates to a method for the inhibition of skin atrophy, epithelial or mucosal atrophy in women, especially women during or after the menopause. The invention also concerns prevention or treatment of atrophy-related symptoms in women, especially women during or after menopause.

10

BACKGROUND OF THE INVENTION

The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details respecting the practice, are incorporated by reference.

During and after menopause, elderly women commonly develop symptoms which are due to estrogen deficiency. These symptoms include hot flashes, sweating, insomnia, depression, vaginal dryness, urinary incontinence, nausea, pain, osteoporosis, coronary heart disease, breast tenderness, oedema, fatigue, decreased sexual activity, as well as subsequent psychosocial problems (Payer, 1990; Rekers, 1990). In addition, estrogens are suggested to have neuroprotective effects. Thus, declining estrogen concentrations may negatively affect the mental activities of aging women (Schneider & Finch, 1997; Wickelgren, 1997). Estradiol is known to be excellent in the treatment of climacteric symptoms, and its use in the treatment of these symptoms is rapidly increasing. However, estrogens cause an increased risk of endometrial and breast cancers. It is possible to decrease the carcinogenicity of endometrial cancer by sequential progestin administration, but the risk of breast cancer is not diminished by progestins. The carcinogenicity risk limits

the length of estrogen replacement therapy, although it would be very useful to continue the therapy long term, due to the protective effects of estrogens in the bone, in the cardiovascular system, in the central nervous system, and for urinary symptoms.

5

“SERM“s (selective estrogen receptor modulators) have both estrogen-like and antiestrogenic properties (Kauffman & Bryant, 1995). The effects may be tissue-specific as in the case of tamoxifen and toremifene which have estrogen-like effects in the bone, partial estrogen-like effect in the uterus and

10 liver, and pure antiestrogenic effect in breast cancer. Raloxifene and droloxifene are similar to tamoxifen and toremifene, except that their

antiestrogenic properties dominate. Based on the published information, all SERMs are more likely to cause menopausal symptoms than to prevent them.

They have, however, other important benefits in elderly women: they

15 decrease total and LDL cholesterol, thus diminishing the risk of cardiovascular diseases, and they may prevent osteoporosis and inhibit breast cancer growth in postmenopausal women. There are also almost pure antiestrogens under development. They are mainly aimed at the treatment of breast cancer (Wakeling & Bowler, 1988).

20

The compound (deaminohydroxy)toremifene, which also is known under the code FC-1271a or the generic name ospemifene, has relatively weak estrogenic and antiestrogenic effects in the classical hormonal tests (Kangas, 1990). It has antiosteoporosis actions and it decreases total and LDL

25 cholesterol levels in both experimental models and in human volunteers

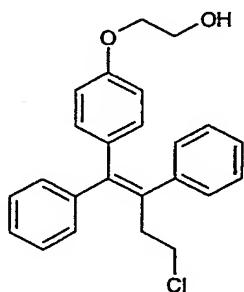
(International patent publications WO 96/07402 and WO 97/32574). It also has antitumor activity in an early stage of breast cancer development in an animal breast cancer model. Ospemifene is the first SERM which has been shown to have beneficial effects in climacteric syndromes in healthy women.

30

The European patent application EP 664124 A1 suggests the use of raloxifene or related compounds for the inhibition of skin atrophy or vaginal atrophy, especially in postmenopausal women.

5 SUMMARY OF THE INVENTION

According to one aspect, this invention concerns a method for inhibition of skin atrophy, or epithelial or mucosal atrophy in women, said method comprising administering to the woman an effective amount of the compound
10 of formula (I)

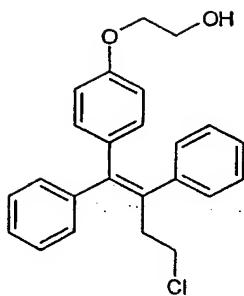


(I)

15

or a geometric isomer, a stereoisomer, a pharmaceutically acceptable salt, an ester thereof or a metabolite thereof.

According to another aspect, this invention concerns a method for treatment
20 or prevention of symptoms related to skin atrophy, or to epithelial or mucosal atrophy in women, said method comprising administering to the woman an effective amount of the compound of formula (I)



(I)

5 or a geometric isomer, a stereoisomer, a pharmaceutically acceptable salt, an ester thereof or a metabolite thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

10 Figures 1A to 1D show changes (from start to 12 weeks' treatment) in the karyopyknosis index for superficial cells of the vaginal epithelium for the individuals treated daily with 30 mg ospemifene, i.e. FC-1271a (1A), 60 mg FC-1271a (1B), 90 mg FC-1271a (1C), and 60 mg raloxifene (1D).

15 DETAILED DESCRIPTION OF THE INVENTION

The methods according to this invention are particularly useful for women during or after the menopause. However, the methods according to this invention is not restricted to women in this age group.

20

This invention relates particularly to the use of the estrogen receptor modulator ospemifene in women during or after the menopause. Ospemifene is the Z-isomer of the compound of formula (I) and it is one of the main metabolites of toremifene, is known to be an estrogen agonist and antagonist

(Kangas, 1990; International patent publications WO 96/07402 and WO 97/32574).

The term "metabolite" shall be understood to cover any
5 (deaminohydroxy)toremifene metabolite already discovered or to be
discovered. As examples of such metabolites can be mentioned the oxidation
metabolites mentioned in Kangas (1990) on page 9 (TORE VI, TORE VII,
TORE XVIII, TORE VIII, TORE XIII), especially TORE VI and TORE
XVIII, and other metabolites of the compound.

10 The wording "inhibition of skin atrophy or epithelial atrophy or mucosal
atrophy" is not limited to complete inhibition of said conditions. It shall be
understood to include also essential alleviation of such conditions.

15 The use of mixtures of isomers of compound (I) shall also be included in this
invention.

A particular form of atrophy to be inhibited is urogenital atrophy. Symptoms
related to urogenital atrophy can be divided in two subgroups: urinary
20 symptoms and vaginal symptoms.

As examples of urinary symptoms can be mentioned micturition disorders,
dysuria, hematuria, urinary frequency, sensation of urgency, urinary tract
infections, urinary tract inflammation, nocturia, urinary incontinence, urge
25 incontinence and involuntary urinary leakage.

As examples of vaginal symptoms can be mentioned irritation, itching,
burning, malodorous discharge, infection, leukorrhea, vulvar pruritus, feeling
of pressure and postcoital bleeding.

The effect of atrophy of the skin is cosmetic, but can also be associated with pathological conditions such as decreased ability of the skin to undergo wound healing. Atrophy or aging of skin appears as change of smoothness and texture causing roughness in look and feel on the outer surface of the skin, change of elasticity of the skin effecting the mechanical properties of the skin, and changes in skin pigmentation. Skin aging in postmenopausal women can also be measured as decrease in the mitotic rate of keratinocytes, changes in dermal thickness and decrease in glucosaminoglycans and soluble collagen which are linked to the moisture content of the skin.

10

The new and surprising effect of ospemifene was found in a clinical study. In this study, raloxifene (60 mg/day) or ospemifene at different doses were given to elderly female volunteers for a period of 3 months. At the dose levels of 30, 60 and 90 mg of ospemifene daily, a significant decrease in vaginal atrophy was observed. These properties are new and unique among the known selective estrogen receptor modulators (SERMs) and indicate that ospemifene at the doses from 25 mg to slightly lower than 100 mg daily, particularly 30 to 90 mg daily, can be successfully used to alleviate symptoms derived from atrophy, especially urogenital atrophy in women during or after the menopause. Furthermore, ospemifene has a superior profile of estrogenic and antiestrogenic effects when compared to any known antiestrogen or SERM compound.

25 The compound (I) can according to this invention be administered by various routes such as oral, topical, transdermal, intravaginal or subcutaneous routes. of which oral or transdermal administration routes are the most preferable.

30 Suitable preparation forms include for example tablets, capsules, granules, powders, suspensions, syrups and transdermal formulations, ointments, creams, or gels. Also subcutaneous implants may be useful for prolonged use.

For vaginal local delivery vaginal creams, gels, vagitories, vaginal tablets, pessaries or vaginal rings are preferred.

EXPERIMENTS

5

A clinical phase I-II study was carried out to study the effects of ospemifene on endometrial thickness, endometrial pathology, (biopsy taken by curettage as described by Vuopala et al, 1982) and cervical smear in healthy postmenopausal female volunteers in the age range 55 to 69 years.

10 Tolerability and pharmacokinetics were also assessed. Raloxifene (60 mg daily) was used as reference. Ospemifene was given perorally at the doses of 30, 60 and 90 mg daily. There were 29 volunteers at each dose level, as well as in the raloxifene group. Ospemifene was administered in gelatine capsules containing either 30, 60 or 90 mg of ospemifene. The thickness of the 15 endometrium was evaluated by ultrasonography using a Hitachi EUB-405 instrument. The vaginal epithelium was assessed by karyopyknosis index which is a well known assessment method among the skilled persons. In this method, the vaginal fraction of the cervical smears is estimated as the percentage of the number of cells from different layers: the parabasal cell 20 layer; the intermediate cell layer; and the superficial cell layer. Estrogenicity is seen by a shift towards superficial cell fraction. In postmenopausal women this fraction usually is close to zero and estradiol treatment increases the fraction close to 100. Samples were taken before and after the treatment (at 3 months).

25

Assessment of the vaginal estrogenic effect of ospemifene

30 Table 1 below shows the change in maturity index for parabasal cells (MI 1) and maturity index for superficial cells (MI 3), after 3 months' administration of varying doses of ospemifene or raloxifene.

Table 1. Change in maturity index for parabasal cells (MI 1) and maturity index for superficial cells (MI 3), after 3 months' administration of varying doses of ospemifene or raloxifene. (MI 1: index 100 no estrogenicity; index 0 full estrogen, and MI 3: index 100 full estrogen; index 0 no estrogenicity).

5

| Compound and dose | MI 1 mean | MI 1 Sd | MI 3 mean | MI 3 sd |
|---------------------------|--------------|------------|--------------|------------|
| Ospemifene, 30 mg, (n=21) | -40 | 42 | +12.4 | 13.6 |
| Ospemifene, 60 mg, (n=20) | -26 | 39 | +5.5 | 13.4 |
| Ospemifene, 90 mg, (n=22) | -48 | 44 | +12.5 | 14.0 |
| Raloxifene, 60 mg, (n=19) | -2 | 34 | -0.3 | 4.1 |

10 In Figures 1A to 1D there are shown changes (from start to 12 weeks' treatment) in the karyopyknosis index for superficial cells of the vaginal epithelium for the individuals treated daily with 30 mg ospemifene (1A), 60 mg ospemifene (1B), 90 mg ospemifene (1C), and 60 mg raloxifene (1D). In the Figures, the code FC-1271a is used instead of the generic name

15 ospemifene.

Cervical smear assessments indicate that no one in the raloxifene group (Fig. 1D) had a significant change from baseline to post-treatment in the karyopyknosis index for superficial cells. Most of the individuals in the ospemifene groups had slight increases in the index, but in rest of the 5 subjects the estrogenic effect was very weak, if measurable at all. In all cases the increase was small (< 40 except for one case which was 45 in the 90 mg group) when compared to estradiol which is known to increase the index virtually by 100. A weak but statistically significant estrogenic effect in the cervical smear was therefore documented. No pathological changes were seen 10 in any sample.

Assessment of the endometrial estrogenic effect of ospemifene

Ospemifene had a weak estrogenic effect on endometrial histology. This 15 effect is clearly weaker than that seen with estrogen replacement therapy. There were no malignant findings in the endometrium. The thickness of the endometrium as assessed by ultrasonography showed only a minor, statistically not significant, increase in the thickness (average 0.2 mm, 0.5 mm and 0.5 mm) at the dose levels of 30, 60 and 90 mg, respectively. The 20 measured values were always smaller than 8 mm, which is considered to be a thickness which is indicative for a physiologically significant estrogenicity of SERMs like tamoxifen (Hann et al, 1997; Lahti et al, 1993).

Effect on urogenital atrophy and symptoms related thereto

25 In the clinical phase I and II studies, 241 posmenopausal women have been treated with ospemifene. 77 were treated with 25-30 mg, 78 with 50-60 mg, 78 with 90-100 mg and 8 with 200 mg daily dose of ospemifene. In the 30 control groups, 47 were treated with placebo and 29 with raloxifene. Some of the subjects reported spontaneously alleviation of the symptoms associated

with urogenital atrophy. The symptoms include both vaginal and urinary symptoms such as vaginal discomfort with irritation, itching, burning, smarting, postcoital bleeding, vulvar itching and/or malodorous discharge and leukorrhea. The urinary symptoms alleviated in individual cases include

5 urinary incontinence, recurrent urinary tract infections, micturition disorders, urinary frequency, nocturia, sensation of urgency, urge incontinence and involuntary urinary leakage. Also, the clinicians reported cases where signs of urogenital atrophy, such as vaginal pallor, petechiae, friability, vaginal mucosa atrophy and ulceration were alleviated by ospemifene.

10

Based on the present data, the optimal clinical dose is expected to be higher than 25 mg daily and lower than 100 mg daily. A particularly preferable daily dose is found in the range 30 to 90 mg. At the higher doses (100 and 200 mg daily), ospemifene shows properties more similar to those of tamoxifen and 15 toremifene. Ospemifene is an especially valuable drug because it has an excellent tolerability. In addition, ospemifene decreases total and LDL cholesterol, increases HDL cholesterol, and prevents osteoporosis and early stage breast cancer. The present invention suggests that ospemifene and other compounds of formula (I) can be also used during menopause as hormone 20 replacement therapy instead of estrogens, which are known to increase the risk of breast and endometrium cancers.

It will be appreciated that the methods of the present invention can be incorporated in the form of a variety of embodiments, only a few of which are 25 disclosed herein. It will be apparent for the expert skilled in the field that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

REFERENCES

Delmas PD, Bjarnason NH, Mitlak BH, Ravoux AC, Shah AS, Huster WJ,
Draper M, Christiansen C: Effects of raloxifene on bone mineral density,
5 serum cholesterol concentrations, and uterine endometrium in
postmenopausal women. *N Engl J Med* 337: 1641-1647, 1997

Ettinger B, Genant HK, Cann CE: Long-term estrogen replacement therapy
prevents bone loss and fractures. *Ann Intern Med* 102: 319-324, 1985
10

Hann LE, Giess CS, Bach AM, Tao Y, Baum HJ, Barakat RR: Endometrial
thickness in tamoxifen-treated patients: correlation with clinical and
pathologic findings. *Am J Roentgenol* 168: 657-661, 1997

Gustafsson J-Å: Estrogen receptor β - getting in on the action? *Nature Medicine* 3: 493-494, 1997
15

Kangas L: Biochemical and pharmacological effects of toremifene
metabolites. *Cancer Chemother Pharmacol* 27: 8-12, 1990

Kauffman RF, Bryant HU: Selective estrogen receptor modulators. *Drug News Perspect* 8: 531-539, 1995
20

Lahti E, Blanco G, Kauppila A, Apaja-Sarkkinen M, Taskinen PJ,
Laatikainen T: Endometrial changes in postmenopausal breast cancer patients
receiving tamoxifen. *Obstet Gynecol* 81: 660-664, 1993
25

Palkowitz AD, Glasebrook AL, Thraser KJ, Hauser KL, Short LL,
Phillips DL, Muchi BS, Sato M, Shetler PK, Cullinan GJ, Pell TR, Bryant
30 HU: Discovery and synthesis of [6-hydroxy-3-[4-[2-(1-

piperidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene: a novel, highly potent, selective estrogen receptor modulator. *Med Chem* 40: 1407-1416, 1997

5 Payer L: The menopause in various cultures. In: *A portrait of the menopause. Expert reports on medical and therapeutic strategies for the 1990s*. Ed. Burger H & Boulet M, Parthenon Publishing, Park Ridge, NJ, USA, 1991. pp 3-22

10 Rekers H: Mastering the menopause. In: *A portrait of the menopause. Expert reports on medical and therapeutic strategies for the 1990s*. Ed. Burger H & Boulet M, Parthenon Publishing, Park Ridge, NJ, USA, 1991. pp 23-43

Schneider LS, Finch CE: Can estrogens prevent neurodegeneration. *Drugs & Aging* 11: 87-95, 1997

15 Spector IP, Carey MP: Incidence and prevalence of sexual dysfunctions: a critical review of the empirical literature. *Archives of Sexual Behaviour* 19: 389-408, 1990.

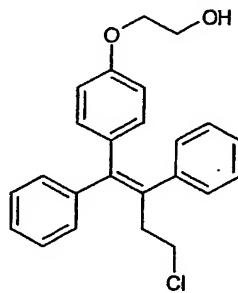
20 Vuopala S, Kauppila A, Mikkonen M, Stenbäck F: Screening of asymptomatic postmenopausal women for gynecological malignancies, with special reference to endometrial sampling methods. *Arch Gyncol* 231: 119-127, 1982

25 Wakeling AE, Bowler J: Biology and mode of action of pure antiestrogens. *J Steroid Biochem* 30: 1-6, 1988

Wickelgren I: Estrogen stakes claim to cognition. *Science* 276: 675-678, 1997

CLAIMS

1. A method for inhibition of skin atrophy, or epithelial or mucosal atrophy in women, said method comprising administering to the woman an effective amount of the compound of formula (I)



10

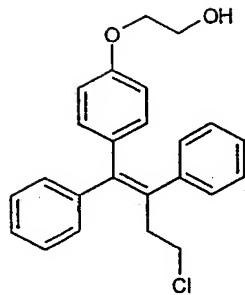
(I)

or a geometric isomer, a stereoisomer, a pharmaceutically acceptable salt, an ester thereof or a metabolite thereof.

15 2. The method according to claim 1 wherein compound (I) is ospemifene.

3. The method according to claim 1 or 2 wherein the atrophy is urogenital atrophy.

20 4. A method for treatment or prevention of symptoms related to skin atrophy, or to epithelial or mucosal atrophy in women, said method comprising administering to the woman an effective amount of the compound of formula (I)



(I)

5 or a geometric isomer, a stereoisomer, a pharmaceutically acceptable salt, an ester thereof or a metabolite thereof.

5. The method according to claim 4 wherein compound (I) is ospemifene.

10 6. The method according to claim 1 wherein the atrophy is urogenital atrophy.

7. The method according to claim 6 wherein the symptoms are urinary symptoms.

15 8. The method according to claim 7 wherein the urinary symptoms are micturition disorders, dysuria, hematuria, urinary frequency, sensation of urgency, urinary tract infections, urinary tract inflammation, nocturia, urinary incontinence, urge incontinence or involuntary urinary leakage.

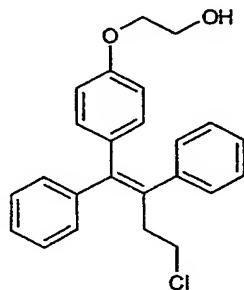
20 9. The method according to claim 6 wherein the symptoms are vaginal symptoms.

10. The method according to claim 9 wherein the vaginal symptoms are irritation, itching, burning, malodorous discharge, infection, leukorrhea, vulvar pruritus, feeling of pressure or postcoital bleeding.

5 11. The method according to claims 1 or 4 wherein compound (I), its isomer, salt or ester is administered orally, topically, transdermally, intravaginally or subcutaneously.

12. Use of the compound of formula (I)

10



(I)

15

or a geometric isomer, a stereoisomer, a pharmaceutically acceptable salt, an ester thereof or a metabolite thereof for the manufacture of a pharmaceutical composition for inhibition of skin atrophy, or epithelial or mucosal atrophy in women.

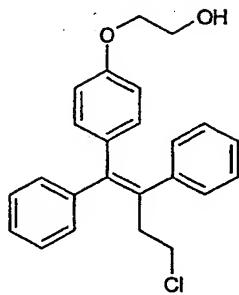
20

13. The use according to claim 12 wherein compound (I) is ospemifene.

14. The use according to claim 12 or 13 wherein the atrophy is urogenital atrophy.

25

15. Use of the compound of formula (I)



5

(I)

or a geometric isomer, a stereoisomer, a pharmaceutically acceptable salt, an ester thereof or a metabolite thereof for the manufacture of a pharmaceutical composition for treatment or prevention of symptoms related to skin atrophy, or to epithelial or mucosal atrophy in women.

16. The use according to claim 15 wherein compound (I) is ospemifene.

15 17. The use according to claim 12 wherein the atrophy is urogenital atrophy.

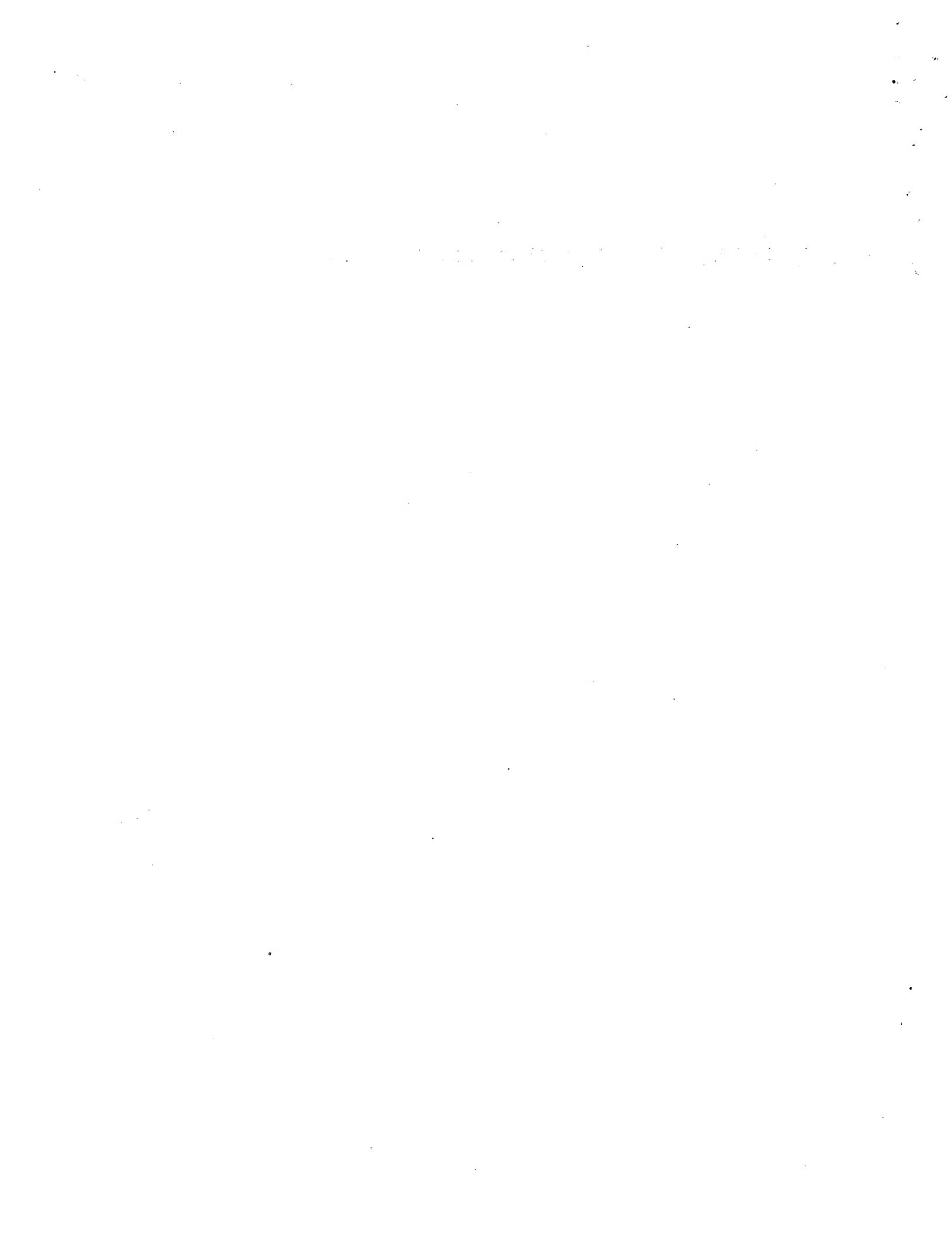
18. The use according to claim 17 wherein the symptoms are urinary symptoms.

20 19. The use according to claim 18 wherein the urinary symptoms are micturition disorders, dysuria, hematuria, urinary frequency, sensation of urgency, urinary tract infections, urinary tract inflammation, nocturia, urinary incontinence, urge incontinence or involuntary urinary leakage.

20. The use according to claim 17 wherein the symptoms are vaginal symptoms.

21. The use according to claim 20 wherein the vaginal symptoms are
5 irritation, itching, burning, malodorous discharge, infection, leukorrhea,
vulvar pruritus, feeling of pressure or postcoital bleeding.

22. The use according to claims 12 or 15 wherein compound (I), its isomer,
salt or ester is administered orally, topically, transdermally, intravaginally or
10 subcutaneously.



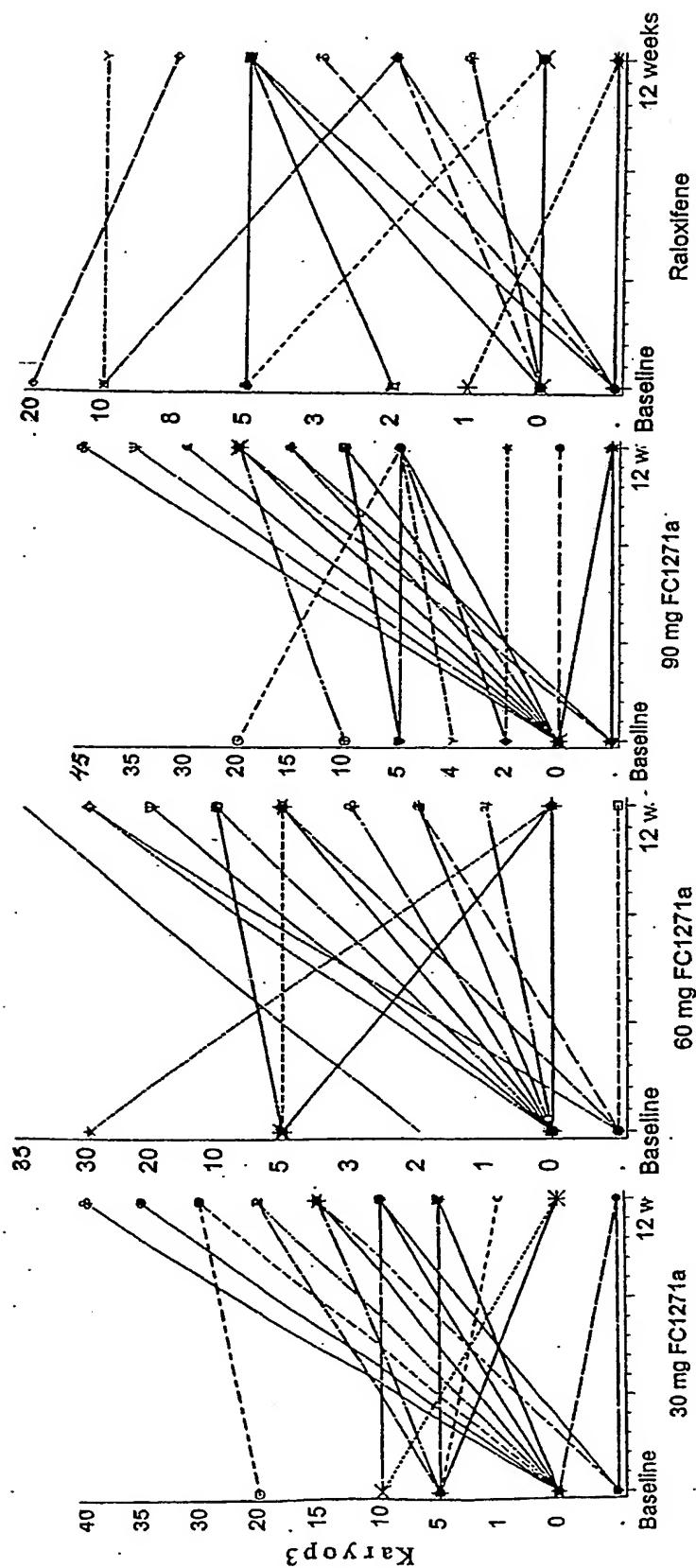
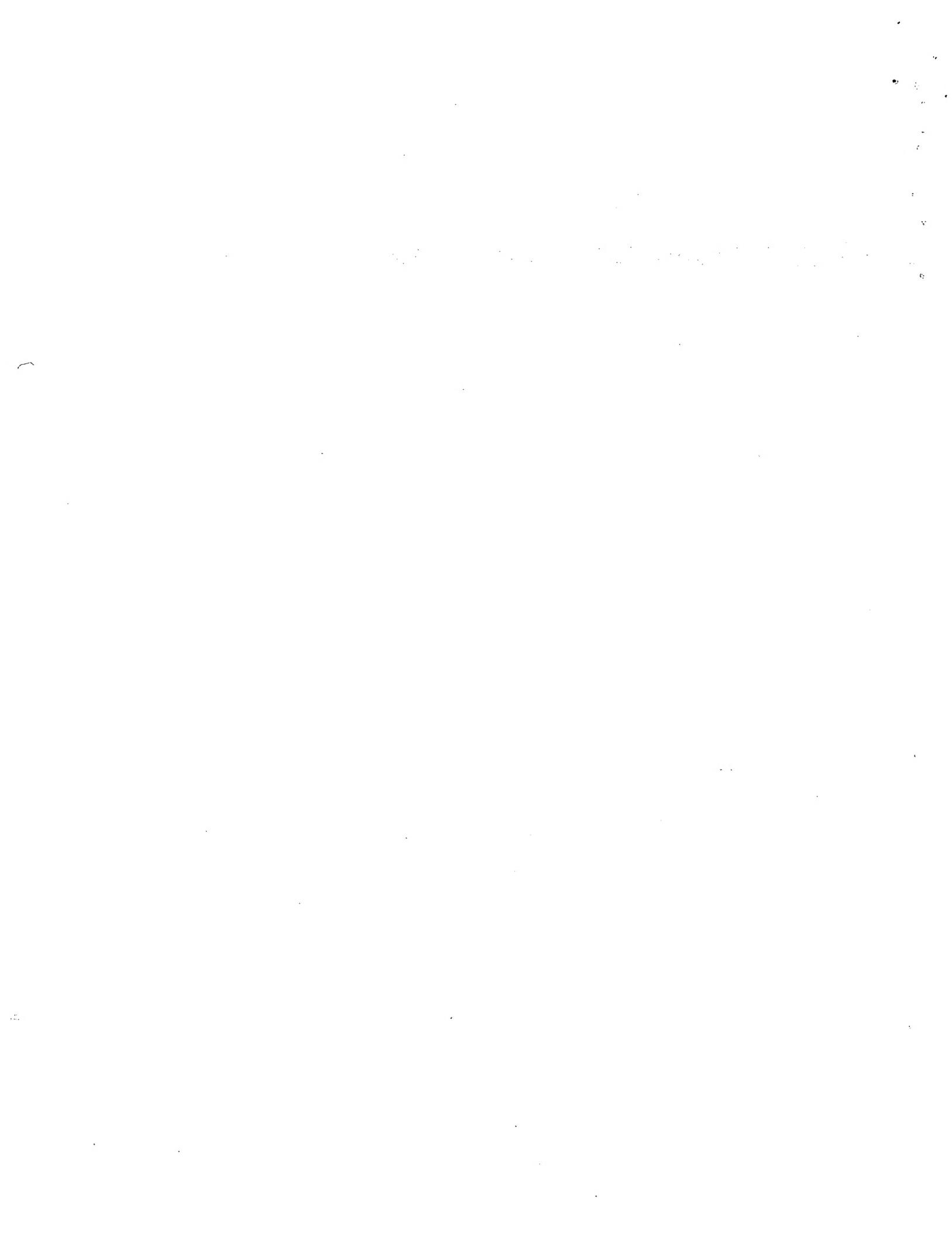


FIG. 1A

FIG. 1B

FIG. 1C

FIG. 1D



INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 03/00369

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/085

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| X | WO 0207718 A1 (HORMOS MEDICAL CORPORATION), 31 January 2002 (31.01.02) -- | 1-22 |
| A | US 5352699 A (CONNIE JACKSON), 4 October 1994 (04.10.94), see "Background of the invention" -- | 1-22 |
| A | US 5747059 A (NIELS KORSGAARD ET AL), 5 May 1998 (05.05.98), see "Background of the invention" -- | 1-22 |
| A | US 2001034340 A1 (JAMES H. PICKAR), 25 October 2001 (25.10.01), see "Background" ----- | 1-22 |

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

19 August 2003

26-08-2003

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. + 46 8 666 02 86Authorized officer
Göran Karlsson/EÖ
Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI03/00369

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 1-11
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI03/00369

Claims 1-11 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

26/07/03

PCT/FI 03/00369

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|--|------------------|-------------------------|--|------------------|
| WO 0207718 A1 | 31/01/02 | AU 5844901 A | | 05/02/02 |
| | | BR 0112659 A | | 24/06/03 |
| | | CA 2416480 A | | 31/01/02 |
| | | CZ 20030026 A | | 14/05/03 |
| | | EP 1305014 A | | 02/05/03 |
| | | NO 20030273 A | | 20/01/03 |
| | | US 6245819 B | | 12/06/01 |
| | | US 2003036566 A | | 20/02/03 |
| US 5352699 A | 04/10/94 | NONE | | |
| US 5747059 A | 05/05/98 | AU 1367397 A | | 01/08/97 |
| | | CA 2241556 A | | 17/07/97 |
| | | EP 0873121 A | | 28/10/98 |
| | | JP 2000506506 T | | 30/05/00 |
| | | WO 9725036 A | | 17/07/97 |
| | | ZA 9700169 A | | 21/07/97 |
| US 2001034340 A1 | 25/10/01 | AU 5003401 A | | 03/10/01 |
| | | BG 107095 A | | 30/05/03 |
| | | BR 0109334 A | | 24/12/02 |
| | | CA 2402983 A | | 27/09/01 |
| | | CN 1418102 T | | 14/05/03 |
| | | CZ 20023162 A | | 12/03/03 |
| | | EP 1265616 A | | 18/12/02 |
| | | NO 20024478 A | | 19/09/02 |
| | | WO 0170208 A | | 27/09/01 |